PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/008114	20.07.2004	21.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07K14/54, C07K14/55, C12N15/62, C12N15/861, A61K48/00, A61K38/19

Applicant
TRANSGENE S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Authorized Officer

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-41, as far as they relate to fusion proteins based on IL-7, IL-15, IL-21, IL-27, IL-31, IFNg

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. cf. above

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-41 as far as they relate to fusions of IL-2 with IL-7, and IL-18 with IL-2

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-41
	No:	Claims	1-6
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-41
Industrial applicability (IA)	Yes:	Claims	1-41
	No:	Claims	

2. Citations and explanations

   see separate sheet

1. Unity of the invention

A non-unity objection has been raised. The following assessment relates to searched Inventions 1 and 10, i.e. to fusion proteins comprising Il-2 and IL-7, and IL-18 and IL-2, respectively.

2. Fusions of IL-2 and IL-7

2.1 Novelty (Art. 33(2) PCT)

Claims 1 to 5 lack novelty in view of the cited prior art disclosing IL-2 fusions with Il-2, IL-6, GM-CSF and IFNgamma (or IFNg with IL-2).
Fusions proteins comprising Il-2 and IL-7 have not been disclosed in the cited prior art.
Therefore, the claims are new to the extent that they relate to invention 1.

2.2. Inventive step (Art. 33(3) PCT)

XP009040509 (Kaufmann et al.) and XP009040510 (Kondo et al.) describe beneficial effects for the combination of Il-2 with IL-7 in the treatment or prevention of tumors.
Fusion proteins of a number of immunoregulatory peptides have been described in a number of prior art documents.
As discussed on pp. 5/6 of the instant application, the benefits of fusing cytokines were known to the person of skill (cf. also the cited X-docs). Therefore, and in view of he afore mentioned XP documents, the ISA cannot recognize anything inventive in specifically fusing IL-2 with IL-7.
Expression of Il-2 fusion proteins in adenoviral and other vectors has been known (WO94/21792, WO98/40498, WO99/36440). Coexpression of one or more interleukins by viral vectors in combination with antigens (e.g. HPV) has been described (WO98/08947, p. 19). Likewise, IL-2 mutants with improved activities were known (cf. Shanafelt et al., WO99/60128, WO93/20849, all cited in the application).
Gene therapy with CDase in combination with IL-2 has been described in Ju et al., and adenoviral vectors expressing a fused CDase-UPRTase is disclosed in US6552005.
The ISA is of the opinion that in view of he demonstrated ability of adenoviral vectors to express IL-2 fusion proteins, the expression specifically of IL-2 - IL-7 fusions did not

As far as the claims relate to variant IL-2 or IL-18, they are considered obvious in view of WO02/101049, WO99/60128, and WO93/20849.
Adenoviral vectors were known in the art (WO01/68896, Wang et al.), as well as the use of IL-2 in combination with IL-18 to treat infections or cancer.